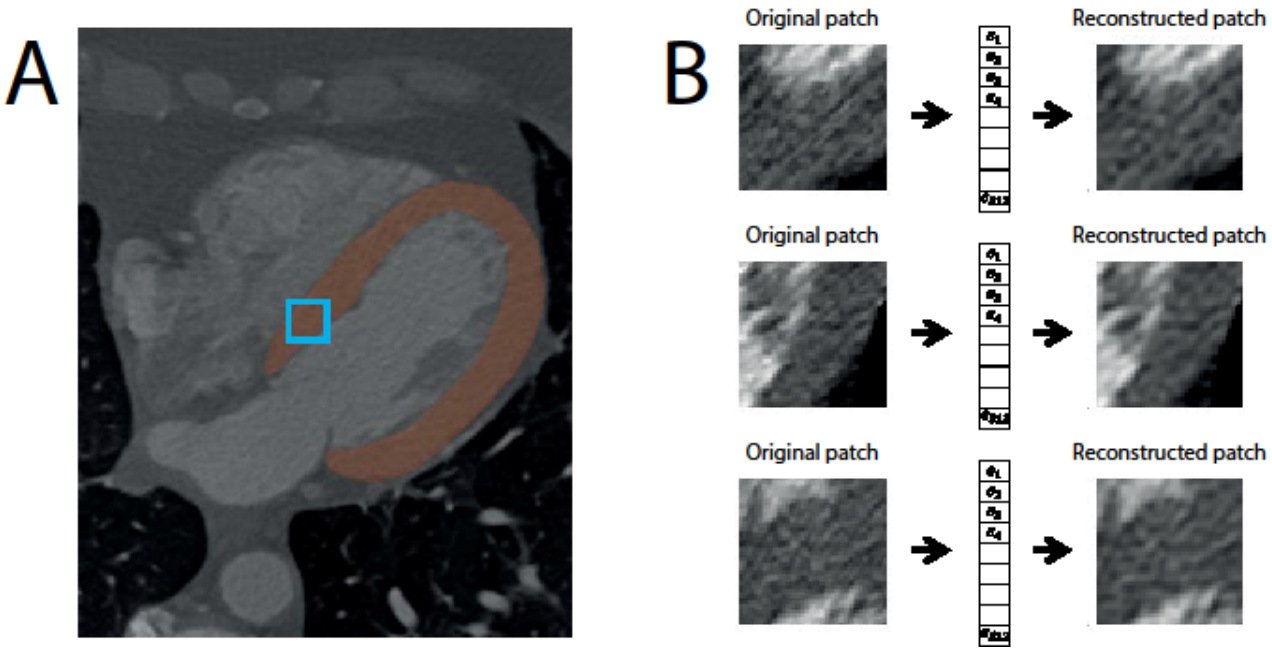
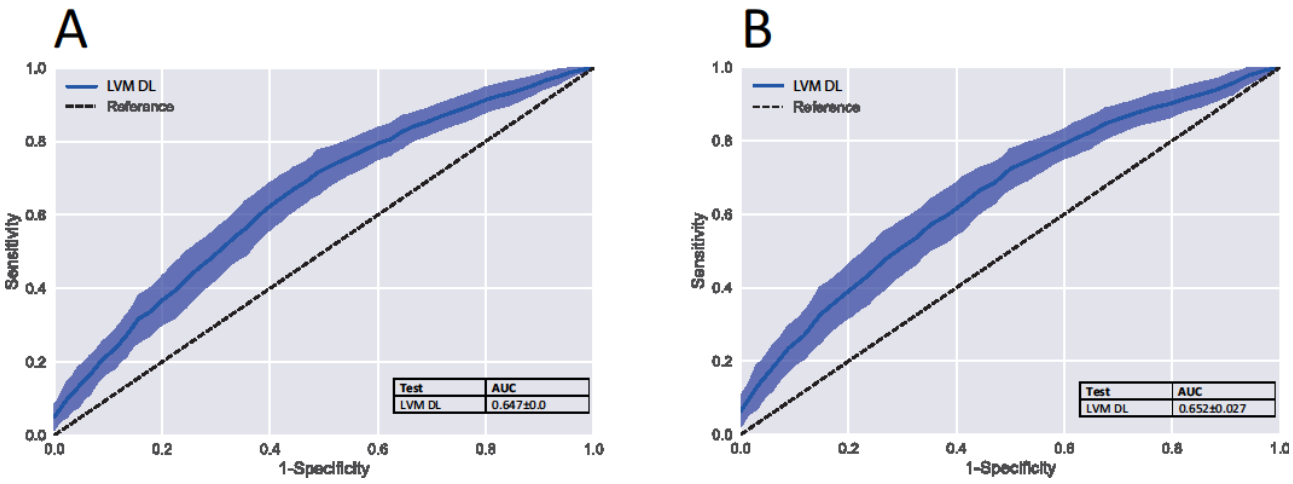
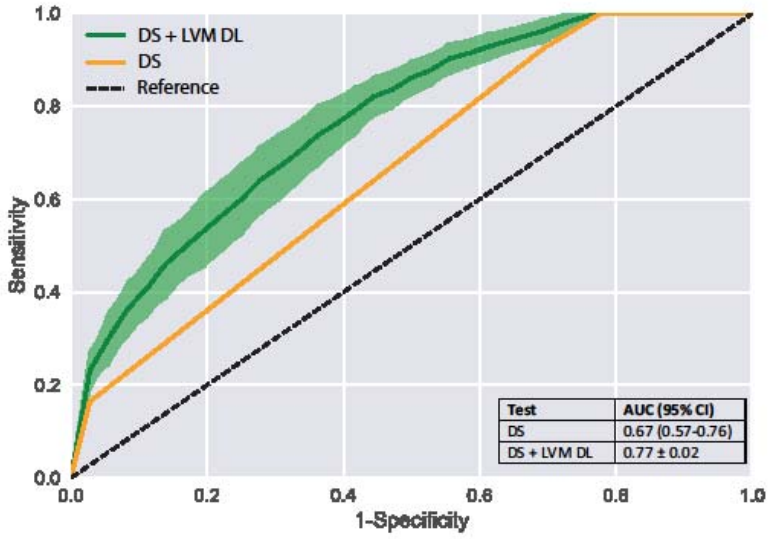


Supplement Figure 1. Encoding the LVM in the DL method using a convolutional auto-encoder. Because the discriminative features of the LVM for functionally significant stenosis on CCTA at rest are not well-defined, we applied an unsupervised approach using a convolutional auto-encoder (CAE). Unlike most studies, where features were designed by hand, in the current study features were based on the encodings extracted in an unsupervised fashion by the DL method using a CAE. To ensure that these encodings represent the myocardium and not another random organ or structure, only small local image patches of the segmented myocardium (A) were introduced to the CAE and thereafter encoded (B). All voxels of the segmented myocardium in all slices were encoded by the CAE using patches around them, as illustrated by an example patch (blue box) in A. To ensure that the extracted encodings would be relevant in representing the myocardial patches, the CAE was trained by forcing it to reconstruct (decode) the input myocardium patches using only these encodings, as illustrated by three randomly selected patches in B. To train the CAE, the input myocardial patches were compressed (encoded) to N=512 values (encodings) and reconstructed (decoded) back. The mean squared error between the input patches and the reconstructed patches was computed during training and minimized iteratively. This minimization forced the encodings to contain relevant information; successfully representing the myocardium appearance.



Supplement Figure 2. Receiver operating characteristic curves of DL applied to all patients (A, n=126) and patients with intermediate stenosis only (B, n=101). To evaluate robustness of the DL analysis on low- or high-grade stenosis, we also evaluated the performance of our DL algorithm on the complete cohort (n=126). We retrained and evaluated the DL method on all 126 cases using the same scheme of 10-fold cross-validation with 50 repetitions. The resulting ROC curve and AUC are shown in A. These results are comparable with the performance of DL on the intermediate stenosis only (n=101), used in the current study and shown in B. This indicates that comparable discriminative power (but also comparable misclassification) are achieved by the DL algorithm, regardless of the population. However, it should be noted that the entire dataset is obtained from a heavily diseased patient cohort, and thus none of these patients are considered as an "easy case" for classification. *AUC = area under the receiver operating characteristic curve; DL = deep learning; LVM = left ventricular myocardium; ROC = receiver operating characteristic*



Supplement Figure 3. Receiver operating characteristic curves for patients without prior MI, CABG and/or PCI (n=103). Diagnostic performance of DS and a combination of DL added to DS from CCTA for predicting functionally significant stenosis on a patient basis. For the combined method, ROC-curves and AUC are depicted as average ± SD of 50 cross-validation experiments. *AUC = area under the receiver operating characteristic curve; CABG = coronary artery bypass grafting; CCTA = coronary computed tomography angiography; DL = deep learning; DS = degree of stenosis; LVM = left ventricular myocardium; MI = myocardial infarction; PCI = percutaneous coronary intervention; ROC = receiver operating characteristic*

Supplement Table 1. Diagnostic performance for patients without prior MI, CABG and/or PCI (n=103).

Method and threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
CCTA ≥25% DS	100.0 (67/67) [94.6-100.0]	22.2 (8/36) [10.1-39.2]	70.5 (67/95) [66.8-74.0]	100.0 (8/8) [100.0-100.0]	72.8 (75/103) [64.1-81.6]	0.67 [0.57-0.76]
CCTA ≥50% DS	92.5 (62/67) [83.4-97.5]	30.6 (11/36) [16.3-48.1]	71.3 (62/87) [66.4-75.7]	68.8 (11/16) [45.3-85.4)	70.9 (73/103) [62.0-79.8]	0.67 [0.57-0.76]
CCTA ≥70% DS	16.4 (11/67) [8.5-27.5]	97.2 (35/36) [85.5-99.9]	91.7 (11/12) [59.7-98.8]	38.5 (35/91) [35.7-41.3]	44.7 (46/103) [34.9-54.4]	0.67 [0.57-0.76]
CCTA DS + DL combined	84.8 ± 0.04	50.5 ± 0.04	76.1 ± 0.02	64.5 ± 0.05	72.8 ± 0.02	0.77 ± 0.02

Data is given in percentage, data in parentheses is raw data and data in brackets is 95% confidence interval. For the combined method, data is depicted as average ± SD of 50 cross-validation experiments.

AUC = Area under the receiver operating characteristic curve, CABG = coronary artery bypass grafting; CCTA = coronary computed tomography angiography; DL = deep learning; DS = degree of stenosis; LVM = left ventricular myocardium; MI = myocardial infarction; NPV = negative predictive value; PCI = percutaneous coronary intervention; PPV = positive predictive value; SD = standard deviation